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MAGUKs: multifaceted synaptic organizers

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Abstract

The PSD-95 family of proteins, known as MAGUKs, have long been recognized to be central building blocks of the PSD. They are categorized as scaffolding proteins, which link surface-expressed receptors to the intracellular signaling molecules. Although the four members of the PSD-95 family (PSD-95, PSD-93, SAP102, and SAP97) have many shared roles in regulating synaptic function, recent studies have begun to delineate specific binding partners and roles in plasticity. In the current review, we will highlight the conserved and unique roles of these proteins.

Introduction

Excitatory synapses are most often localized on dendritic spines, which are abundant small membrane protrusions that decorate dendrites. Excitatory synapses include the postsynaptic density (PSD), a specialized electron dense structure positioned at the distal tip of spine heads. Receptors, adhesion molecules and postsynaptic scaffolding proteins accumulate at the PSD to allow efficient synaptic responses to glutamate released from the presynaptic terminal. Scaffolding proteins serve as a platform to hold together the PSD by binding to postsynaptic receptors, adhesion molecules, and cytoplasmic signaling proteins like protein kinases, phosphatases, and GTPases [1–3]. Membrane-associated guanylate kinases (MAGUKs) are the best studied scaffolding proteins, and findings over the last few years demonstrate that PSD-95 and other MAGUKs play diverse roles in regulating synaptic expression of receptors, synaptic plasticity, and are essential for the basic structure of the PSD itself.

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Conflict of interest statement

Nothing declared.

In this review, we will confine our discussion to the PSD-95 family of MAGUKs, which includes PSD-95, PSD-93, SAP102, and SAP97. Structurally, the four members contain three PSD-95/Discs large/Zona occludens-1 (PDZ) domains, followed by a Src-homology-3 (SH3) domain and a catalytically inactive guanylate kinase (GK) domain [Fig. 1]. While these domains are highly conserved among the various MAGUKs, there are also divergent regions, most notably the distinct N-termini. These multiple protein interaction domains allow MAGUKs to act as a bridge between surface-expressed receptors, channels and adhesion molecules and intracellular signaling proteins, enzymes and cytoskeletal elements. Although some binding partners are conserved among the MAGUKs, others are specific to one family member [Fig. 1]. The prototypic MAGUK is PSD-95, named based on its enrichment at the PSD. Early biochemical studies identified PSD-95 as a primary constituent of the PSD [4] and recent findings show that deleting PSD-95 results in a fragmentation of the PSD [5]. Knockdown of PSD-95, PSD-93 and SAP102 family members causes a profound disintegration of the PSD, solidifying the critical role of MAGUKs in the formation and maintenance of the structure [6*].

Light and electron microscopy data [7, 8] indicate that a significant percentage of synapses contain both PSD-93 and PSD-95. Further exploration with super-resolution microscopy has found that many synapses contain sub-synaptic nanodomains enriched in PSD-95 [9*–12**]. Interestingly, these nanodomains are enriched in both PSD-95 and AMPARs. While several studies have found PSD-93 and PSD-95 to play equivalent roles in trafficking AMPARs [13, 14**], similar PSD-93-enriched nanodomains have not been reported. Given the correlation between PSD-95 nanodomains and AMPAR enrichment, it would be interesting to explore whether other MAGUKs infiltrate PSD-95 nanodomains, and whether similar nanodomains populated by other MAGUKs exist and are enriched in AMPARs.

MAGUKs and synaptic expression of glutamate receptors

A primary function of MAGUKs is to bind to and stabilize proteins at synapses. Many lines of evidence show that MAGUKs regulate the synaptic expression of glutamate receptors. All family members bind directly to GluN2 subunits of NMDARs thereby stabilizing NMDARs at the cell surface [15]. Both GluN2A and GluN2B have a conserved PDZ ligand (−ESDV), which regulates direct high affinity binding to MAGUK family members. Deletion of the –ESDV motif or mutations in that domain within GluN2B disrupt surface and synaptic expression of NMDARs [15, 16]. MAGUKs also regulate the synaptic expression of AMPARs; however, unlike NMDAR binding, PSD-95 indirectly interacts with AMPARs through the auxiliary subunit stargazin (stg) and its related family members, TARPs (Transmembrane AMPA Regulatory Proteins), which are critical for synaptic expression of AMPARs [17, 18]. However, another family member, SAP97, binds directly to the GluA1 AMPAR subunit [19]. Whereas SAP97 can rescue the deficits in AMPAR currents in PSD-93/-95 double-knockout neurons, deleting SAP97 has no effect on synaptic transmission [20].

Early work demonstrated that the phosphorylation of potassium channels in the PDZ ligand [21] disrupted PSD-95 binding. The same is true with the NMDAR/PSD-95 interaction, which is inhibited by phosphorylation. Indeed, there is an intricate interplay between

phosphorylation and synaptic expression of NMDARs. Synaptic activity results in CaMKII binding to GluN2B and recruitment of casein kinase 2 (CK2) into a trimolecular complex [22]. CK2 phosphorylation of the PDZ ligand on S1480 of GluN2B disrupts PSD-95 binding resulting in dramatic reduction in NMDAR surface and synaptic expression [16]. CK2 phosphorylation of the PDZ ligand is an important step in the GluN2B to GluN2A synaptic switch. A nearby endocytic motif on GluN2B (−YEKL) is a target for tyrosine kinases and phosphatases and when phosphorylated, NMDARs are not internalized and surface/synaptic expression is increased. The CK2 phosphorylation of the PDZ ligand and the phosphorylation of the endocytic motif on GluN2B play opposing roles in modulating synaptic NMDARs.

Although MAGUKs are most often thought of as stabilizing synaptic proteins, recent findings show that SAP102 can also play an unanticipated role in clearing NMDARs from synaptic sites [23*]. It is widely accepted that SAP102 is associated with glutamate receptor targeting to synapses during neuronal development [7, 24, 25] and that PSD-95 directly binds to the PDZ ligand of GluN2B and stabilizes its surface expression at synapses [16]. All MAGUKs bind to the –ESDV motif on GluN2 subunits of NMDARs. However, non-PDZ interactions have also been reported [Fig. 1; 23*, 26]. SAP102 binds to the GluN2B C-terminus upstream of the PDZ ligand. This binding event is dependent on the SAP102 unique N-terminal domain, and is regulated by alternative splicing. When GluN2B phosphorylation blocks binding to MAGUKs via its PDZ ligand, it can still bind to SAP102 via this non-conventional binding site, which facilitates the removal of synaptic NMDARs. Because SAP102, unlike PSD-93 and PSD-95, is not palmitoylated [Fig. 1; 27] and has been shown to move in and out of spines [28], it is an ideal protein to shuttle NMDARs in and out of the synapse.

Role for PSD-95 in sculpting protein content at the PSD

In addition to the many roles that MAGUKs play in receptor trafficking, a recent study demonstrates that PSD-95 acts in an unexpected way to regulate the expression of the tyrosine phosphatase PTPN5, also known as STEP (STriatal-Enriched protein tyrosine Phosphatase), in the PSD [29**]. STEP is known to regulate surface expression of NMDARs by dephosphorylating GluN2B Y1472 within the endocytic motif, thereby increasing internalization [30]. Recent data show that PSD-95, but not other MAGUKs, binds to STEP via its PDZ3 domain [Fig. 1; 29**] in a palmitoylation-dependent manner. PSD-95 triggers the degradation of STEP and restricts STEP to a low level in the PSD. Furthermore, PSD-95 knock-down results in a marked increase in synaptic STEP and a decrease in synaptic GluN2B. Similar findings were observed *in vivo* in PSD-95 KO mice. Therefore, there is a PSD-95 specific effect on synaptic NMDARs that is independent of the well-established stabilizing role as a scaffolding protein. It is likely that as we learn more about MAGUKs, additional non-scaffolding roles will be identified.

MAGUK involvement in synaptic transmission

What factors influence MAGUK localization of AMPARs to synapses? There is a linear relationship between PSD diameter and AMPAR number [31], and genetic deletion of

AMPARs does not affect PSD size [32]. This suggests that, on average, the size of the PSD is the primary determinant of AMPAR content. There are, however, other factors that modulate AMPAR synaptic strength. One factor that can be modulated is the affinity of TARPs for MAGUKs. It has been known for some time that TARPs, such as stg, bind AMPARs and link them to MAGUKs via an interaction between MAGUK PDZ-domains and a TARP cytoplasmic tail (c-tail) PDZ-binding motif [17, 33, 34]. One factor limiting this interaction is electrostatic attraction between the TARP c-tail and the lipid membrane, which inhibits binding of stg to PSD-95 [35]. Although phosphorylation of the stg c-tail via CaMKII and PKC has been shown to increase AMPAR EPSCs [36], the mechanism is not fully understood. It has recently been shown that phosphorylation of the stg c-tail disrupts its electrostatic interactions with the membrane [35], dissociating it and extending it into the cytoplasm. Interestingly, this facilitates binding to MAGUK PDZ domains, specifically PDZ domain 3, which had not been thought to play a large role in basal transmission [34]. Binding to PDZ domain 3 leads to increases in the percent of AMPARs at synapses, and in AMPAR-mediated EPSCs [37*]. Since phosphorylation of the stg c-tail occurs via CaMKII and PKC [36], it is tempting to speculate that one component of the AMPAR EPSC increase during LTP is CaMKII-mediated phosphorylation of the stg c-tail. However, recent evidence shows that kainate receptors, which do not interact with TARPs, are competent to mediate LTP [38], indicating that LTP can occur in the absence of this mechanism.

MAGUKs play an established role localizing AMPARs and NMDARs to synapses. RNAi-mediated knockdown of PSD-93, PSD-95 and SAP102 together reduces the size of AMPAR and NMDAR-containing synaptic responses by roughly 75%. Knockdown of PSD-93, PSD-95, or SAP102 individually causes similar reductions in baseline synaptic currents in each case: ~50% for AMPAR-EPSCs and ~25% for NMDAR EPSCs [14**]. Thus, the 3 MAGUKs contribute to basal trafficking of AMPARs and NMDARs to a similar degree.

Although glutamatergic EPSCs are greatly reduced after MAGUK knockdown, dendritic spine density is unchanged, suggesting MAGUKs are responsible for localizing glutamate receptors to synapses, but not for processes involved in spine formation or maintenance [14**]. Furthermore, these and other results indicate that compensatory mechanisms do not change spine density in response to reduced excitatory activity [32]. Together, these data are consistent with a large population of ‘silent’ spines that lack both AMPARs and NMDARs that emerge after MAGUK loss. These data, however, do not rule out changes in spine stability that could occur, for example if an activity-dependent step stabilizes new spines [39]. In particular, smaller-diameter spines, such as those seen after MAGUK loss, have previously been shown to be less stable than larger spines [40].

MAGUK loss triggers a homeostatic process

One long-standing curiosity in the field has been that removal of each MAGUK family member results in an all-or-none loss of AMPARs at individual synapses [13, 41], meaning synapses either lose their entire complement of AMPARs or are unaffected. This manifests itself as a reduction in AMPAR-containing synapses without a reduction in AMPAR synaptic strength at the remaining synapses. Since MAGUKs are at all synapses, it is puzzling how loss of a single family member causes loss of all AMPARs at a subset of

synapses. Previously, this result has been variously interpreted to mean that individual synapses are reliant on either PSD-95 or PSD-93 but not both [13], or that MAGUKs are required for synaptogenesis [41].

Recent research has shown that following MAGUK loss, a compensatory program dependent on signaling though L-type calcium channels maintains synaptic strength at individual synapses [14**]. This synapse-specific homeostatic program cannibalizes a subset of synapses to localize AMPARs to the remaining synapses. Interestingly, AMPARs are added to the remaining synapses until they perfectly match the synaptic strength of unmanipulated controls, despite the large overall reduction in AMPAR EPSCs. One possibility is the shortage of MAGUKs inhibits further increases at individual synapses [8]. These results strongly suggest that individual synapses have a program that determines ‘default’ strength, which is executed at the single-synapse level and complements known examples of cell-level homeostasis. Existing examples of cell-level homeostasis have been proposed to respond to perturbations in L-type channel calcium influx by scaling overall synaptic input while maintaining relative synaptic strengths. These homeostatic programs counteract deviations from a cell-wide activity ‘set-point’ caused, for example, by Hebbian processes such as LTP. Single-synapse homeostasis, in contrast, acts to maintain a set-point at individual synapses, independent of cellular activity levels. Cell-level and single-synapse homeostasis use many of the same proteins, such as GluA2 [42] and CaMKK [43, 44], and potentially are separate consequences of activation of a common non-Hebbian pathway.

A comparison of MAGUK loss to other forms of homeostasis

Are all non-Hebbian ‘homeostatic’ plasticity programs glimpses of a common pathway that regulates synaptic strength? Other homeostatic programs at single synapses have been described that oppose changes in presynaptic input by manipulating AMPAR synaptic strength [45, 46], and have been found to use components of the cell-level homeostasis program [45]. One final process that regulates synaptic strength and is reminiscent of single-synapse homeostasis is distance-dependent scaling (DDS), a process which, like single-synapse and cell-level homeostasis, is dependent on the GluA2 subunit [47]. DDS translates global signaling cues about relative synaptic location, potentially conveyed at least in part by backpropagating action potentials [48], into a synaptic strength gradient to counter the electrotonic effect on distant synapses. Thus synapse strength increases as synapses get further from the cell body, and precisely counteracts increased electrotonic filtering of EPSCs from these distal synapses. Block of DDS results in strong synapses close to the soma with synapses growing weaker as distance from the soma increases. Given that DDS and single-synapse plasticity share reliance on the same signaling pathways and both serve to set synapse strength, it would appear that these phenomena are different facets of the same homeostatic process. The GluA2 subunit is essential for DDS, and backpropagating action potentials trigger dendritic calcium influx [48–50], through voltage-gated calcium channels including L-type channels [51]. Backpropagating action potentials decrease in size as they penetrate the dendritic arbor and the decreasing calcium influx could serve to indicate increasing distance from the soma and result in stronger synapses. However, further experimentation is required to determine the roles that L-type calcium channel signaling and CaMKK potentially play in DDS.

Multiple lines of evidence have established that homeostatic plasticity actively sets baseline synaptic strength at individual post-synaptic specializations. Although the pathways underlying this set point have been seen in multiple contexts and conceptually split into multiple processes, future research into the detailed molecular pathway of homeostatic plasticity is required to determine whether these processes are independent, or rely on one common pathway that can be initiated in many separate contexts.

Conclusions

The MAGUK family of scaffolding proteins performs a complex array of synaptic functions. The developmental differences between PSD-93/PSD-95 and SAP102, with the latter uniquely expressed early in development, were first described over 15 years ago [7]. Current studies are now elucidating the functional differences between MAGUKs hinted at by this differential expression. Examples include SAP102's unanticipated role in clearing NMDARs [23*], PSD-95's role in triggering STEP degradation [29**], and the divergent roles of PSD-93 and PSD-95 in both Hebbian [52] and non-Hebbian plasticity [9]. Ongoing research will almost certainly continue to reveal the mechanisms underlying differential roles [53–55*] of the MAGUKs.

Although there are many examples of heterogeneity within the MAGUK family, all MAGUKs play a basic role at the synapse: localization of glutamate receptors. In this role, each family member plays an equal part [14**]. Even this fundamental shared property has many unresolved questions to explore. What role do MAGUKs play during Hebbian plasticity, and what factors influence this role? How do the non-Hebbian pathways that control AMPAR localization use MAGUKs to modulate synaptic strength? The MAGUKs' central role in sculpting synaptic strength will continue to provide insight into the underlying mechanisms of glutamatergic transmission for years to come.

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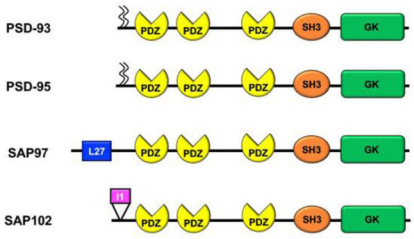
Highlights

- PSD-95 and PSD-93 are essential for PSD structure.
- SAP102 plays a role in clearing NMDARs from the synapse.
- PSD-95 sculpts protein content at the PSD.
- PSD-93 and PSD-95 have divergent roles in both Hebbian and non-Hebbian plasticity.



MAGUK binding proteins		
PSD-93	PDZ1-2:	GluN2B [56], Kir2.3 [57]
	PDZ3:	Neuroligin1-3 [56] , Fyn [58]
	GK:	GKAP [59], MAP1A [60]
	Undefined domain:	Stargazin [61]
PSD-95	PDZ1:	GluK2 [62]
	PDZ1-2:	Shaker-type K+ channel [63], GluN2A-C [64, 65], Kir2.3 [57]
	PDZ1-3:	SynGAP [66], Kalirin-7 [67]
	PDZ2:	Stargazin [17, 68], nNOS [69]
	PDZ3:	β-1 adrenergic receptor [70], Fyn [71], Neuroligin1-3 [56], $STEP_{61}$ [29*]
	SH3:	Pyk2 [72]
	SH3 and GK:	AKAP [73]
	GK:	GKAP [59], SAPAP [74], SPAR [75]
	Undefined domain:	GluK1 [76]
SAP97	PDZ1:	GluK2 [77]
	PDZ1-2:	GluN2A and GluN2B [64], Kir2.3 [57]
	PDZ2:	GluA1 [78], Stargazin [17, 68]
	PDZ3:	Neuroligin1-3 [56]
	SH3 and GK:	AKAP [73]
	GK:	GKAP [59], SAPAP [74], LGN [75]
	Undefinded domain:	GluA2/3 [19]
SAP102	N-terminus:	GluN2B [23*]
	PDZ1-2:	GluN2A-C [65], Kir2.3 [57]
	PDZ3:	Neuroligin1-3 [56], SynGAP [66]
	SH3:	Pyk2 [72]
	Undefined domain:	GluN1 [19], Stargazin [61]

Figure 1. MAGUK family members and their binding proteins

PSD-93 and PSD-95 have two palmitoylation motifs in their N-terminus. L27: Lin2-Lin7; PDZ: PSD-95/Discs large/Zona occludens-1; SH3: Src-homology-3; GK: Guanylate Kinase. SAP102 has a splice variant without the I1 region in the N-terminus.

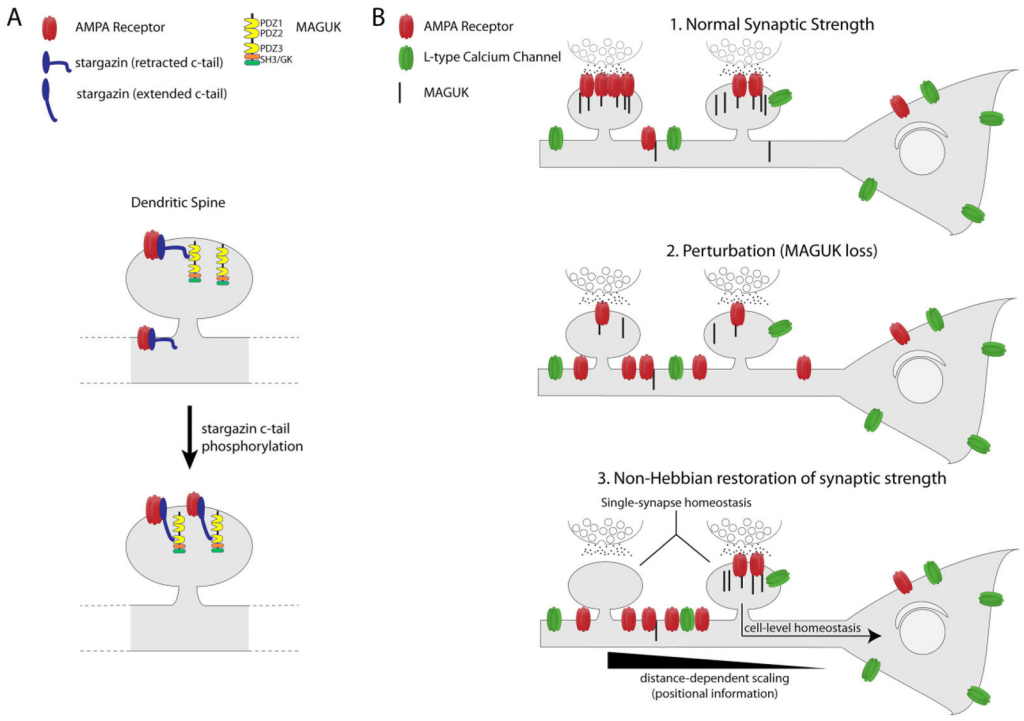


Figure 2. Role of the MAGUKs in Hebbian and non-Hebbian plasticity

The MAGUKs are involved in pathways that set synaptic strength during Hebbian and non-Hebbian plasticity. (A) Phosphorylation of the stargazin c-tail by PKC and CaMKII allows robust binding of the c-tail to the PDZ3 domain of PSD-95. This additional binding site increases the number of synaptically localized AMPARs. (B) MAGUKs set default synaptic strength during non-Hebbian homeostasis. 1. PSD size (and MAGUK content) set baseline ‘default’ synaptic strength. 2. Reduction in MAGUK protein fragments and weakens synapses. 3. Non-Hebbian processes work to restore synaptic strength to a pre-existing set point. These processes include distance-dependent scaling, synapse-level homeostasis, and cell-level homeostatic processes.